LRRK2 Mutant iPSC-Derived DA Neurons Demonstrate Increased Susceptibility to Oxidative Stress.

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Public Summary:
Studies of Parkinson's disease (PD) have been hindered by lack of access to affected human dopamine producing neurons. Here, we report generation of patient-derived induced pluripotent stem cells that carry a common mutation in the Leucine-Rich Repeat Kinase-2 (LRRK2) gene causing familial PD and their differentiation into dopamine neurons. We found that dopamine neurons derived from a patient carrying the LRRK2 mutation showed increased expression of genes that are involved in stress-response of cells and an overexpression of a protein, called alpha-synuclein, highly implicated in the pathogenesis of PD. The mutant neurons were also more sensitive to stress agents, such as hydrogen peroxide and others, than dopamine neurons from control individuals. This enhanced stress sensitivity is consistent with existing understanding of PD disease mechanisms and represents a potential therapeutic target.

Scientific Abstract:
Studies of Parkinson's disease (PD) have been hindered by lack of access to affected human dopaminergic (DA) neurons. Here, we report generation of induced pluripotent stem cells that carry the p.G2019S mutation (G2019S-iPSCs) in the Leucine-Rich Repeat Kinase-2 (LRRK2) gene, the most common PD-related mutation, and their differentiation into DA neurons. The high penetrance of the LRRK2 mutation and its clinical resemblance to sporadic PD suggest that these cells could provide a valuable platform for disease analysis and drug development. We found that DA neurons derived from G2019S-iPSCs showed increased expression of key oxidative stress-response genes and alpha-synuclein protein. The mutant neurons were also more sensitive to caspase-3 activation and cell death caused by exposure to stress agents, such as hydrogen peroxide, MG-132, and 6-hydroxydopamine, than control DA neurons. This enhanced stress sensitivity is consistent with existing understanding of early PD phenotypes and represents a potential therapeutic target.